

Award Number: W81XWH-12-1-0585

TITLE: Intranasal Insulin: A Novel Treatment for Gulf War Multisymptom Illness

PRINCIPAL INVESTIGATOR: Dr. Julia Golier

CONTRACTING ORGANIZATION: Bronx Veterans Medical Research Foundation, Inc.
Bronx, NY 10468

REPORT DATE: October 2015

TYPE OF REPORT: Annual Report

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
<p>Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.</p>					
1. REPORT DATE October 2015		2. REPORT TYPE Annual Report		3. DATES COVERED 30Sep2014 - 29Sep2015	
4. TITLE AND SUBTITLE Intranasal Insulin: A Novel Treatment for Gulf War Multisymptom Illness				5a. CONTRACT NUMBER GW110054	
				5b. GRANT NUMBER GRANT10950728	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Julia Golier E-Mail: Julia.Golier@va.gov				5d. PROJECT NUMBER W81XWH-12-1-0585	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Bronx Veterans Medical Research Foundation, Inc. Bronx, NY 10468				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT Following their deployment to the 1991 Gulf War, many veterans (GWV) reported a constellation of unexplained health symptoms; common among them were attention and memory difficulties, fatigue, joint pain, headaches, gastrointestinal complaints, and mood and sleep problems (Proctor et al., 1998; Sullivan et al., 2003). Despite the passage of time, the symptom complex persists for many veterans. Indeed, it is estimated that at least 25 percent of GWV (nearly 170,000 veterans) have a persistent form of chronic multisymptom illness (CMI) (Kang et al., 2009; Gulf War Research Advisory Committee (RAC), 2008; IOM, 2010). GW deployed veterans are also developing significantly more chronic diseases such as diabetes, hypertension, arthritis, and coronary heart disease than their non-deployed veteran peers (Toomey et al., 2009; Chao et al., 2010; Chao et al., 2011; Li et al., 2011) putting these individuals at risk for accelerated aging-related diseases of the peripheral and central nervous system (CNS). Over the years it has been found that cognitive complaints have been particularly troublesome to GWV. Recent studies have shown a slowing of response speed that affects mental flexibility across multiple cognitive domains (memory, attention, visuospatial functions) especially on tests that were timed and computerized and where small differences in cognitive reaction times could be measured (Anger et al., 1999; RAC, 2008; Krengel and Sullivan, 2008; Toomey et al., 2009; Chao et al., 2011). Recent studies also have suggested that the response inhibition deficits shown in GWV may reflect executive system dysfunction (Tillman et al., 2010) as reflected by slower motor responses across multiple cognitive domains (RAC, 2008). To date, there are no treatments that have been shown to substantially improve cognitive impairments or health symptoms of GWVs. Thus, it is of paramount importance to identify effective, safe, and tolerable treatments for Gulf War CMI.					
15. SUBJECT TERMS Nothing listed					
16. SECURITY CLASSIFICATION OF: a. REPORT U			17. LIMITATION OF ABSTRACT UU	18. NUMBER OF PAGES 6	19a. NAME OF RESPONSIBLE PERSON USAMRMC
b. ABSTRACT U					c. THIS PAGE U

Table of Contents

	<u>Page</u>
Introduction	4
Keywords	4
Overall Project Summary	4
Key Research Accomplishments	5
Reportable Outcomes	5
Conclusion	N/A.
References	6

INTRODUCTION:

Background: Following their deployment to the 1991 Gulf War, many veterans (GWV) reported a constellation of unexplained health symptoms; common among them were attention and memory difficulties, fatigue, joint pain, headaches, gastrointestinal complaints, and mood and sleep problems (Proctor et al., 1998; Sullivan et al., 2003). Despite the passage of time, the symptom complex persists for many veterans. Indeed, it is estimated that at least 25 percent of GWV (nearly 170,000 veterans) have a persistent form of chronic multisymptom illness (CMI) (Kang et al., 2009; Gulf War Research Advisory Committee (RAC), 2008; IOM, 2010). GW deployed veterans are also developing significantly more chronic diseases such as diabetes, hypertension, arthritis, and coronary heart disease than their non-deployed veteran peers (Toomey et al., 2009; Chao et al., 2010; Chao et al., 2011; Li et al., 2011) putting these individuals at risk for accelerated aging-related diseases of the peripheral and central nervous system (CNS). Over the years it has been found that cognitive complaints have been particularly troublesome to GWV. Recent studies have shown a slowing of response speed that affects mental flexibility across multiple cognitive domains (memory, attention, visuospatial functions) especially on tests that were timed and computerized and where small differences in cognitive reaction times could be measured (Anger et al., 1999; RAC, 2008; Krengel and Sullivan, 2008; Toomey et al., 2009; Chao et al., 2011). Recent studies also have suggested that the response inhibition deficits shown in GWV may reflect executive system dysfunction (Tillman et al., 2010) as reflected by slower motor responses across multiple cognitive domains (RAC, 2008). To date, there are no treatments that have been shown to substantially improve cognitive impairments or health symptoms of GWVs. Thus, it is of paramount importance to identify effective, safe, and tolerable treatments for Gulf War CMI.

KEYWORDS: Insulin, clinical trial, novel therapeutics, inflammation, cortisol, chronic fatigue, multi-symptom illness, malaise, deployment.

OVERALL PROJECT SUMMARY:

Objective: To test whether insulin, administered intranasally, improves the health and functioning of GWV with CMI.

Specific Aims: (1) To assess the efficacy of two different doses (10 IU BID and 20 IU BID) of daily intranasal insulin for eight weeks on memory and attention functioning in GWV with CMI. (2) To assess the efficacy of two different doses of intranasal insulin on overall physical health and mood in GWV with CMI. (3) To characterize the effect of two different doses of intranasal insulin on other symptoms that are characteristic of or associated with CMI (e.g., fatigue, pain, sleep quality, subjective cognitive function). (4) To assess the safety of two different doses of self-administered intranasal insulin in GWV with CMI.

Study Design: 114 eligible GWVs with CMI will be randomly assigned in parallel groups to treatment with 20 IU (i.e., 10 IU BID (after breakfast and dinner)), 40 IU (i.e., 20 IU BID (after breakfast and dinner)), or placebo for eight weeks and assessed for clinical outcomes at treatment endpoint. The treatment groups will self-administer 10 IU insulin or 20 IU insulin through

a nasal infusion pump twice daily through the nose. The placebo group will administer saline through a nasal infusion pump twice daily as well. The primary outcome measure will be neuropsychological outcome (verbal memory and selective attention). As this will be the first trial of intranasal insulin in Gulf War veterans, a dose-finding clinical trial is proposed using two doses within the range that has been shown to be effective and safe in cognitively impaired older adults. Treatment duration of eight weeks was chosen in order to assess the effect of sustained intranasal treatment on cognition, mood, and overall health; a post-treatment follow-up assessment will be performed to characterize the sustainability of treatment effects.

KEY RESEARCH ACCOMPLISHMENTS:

All study sites have now obtained the necessary authorizations prior to initiation of human subjects' research. Following the assignment of two site research monitors – Eran Chemerinski, MD at the Bronx VA and Neil Kowall, MD at the Boston VA, all local IRBs approved the revised protocol. All local IRBs also approved the revised consent form following the addition of a DHHS-approved Certificate of Finally, the Boston VA upgraded study status to "greater than minimal risk" per HRPO regulations. All sites have now received HRPO approval.

All previous concerns regarding the intranasal device – control of spray volume, cleaning, securing of internal needle, elimination of battery's thirty-minute "warm-up" period by converting to power adapter – have now been resolved. The budget office has submitted final payment and the site pharmacies await delivery of devices.

Lastly, the REDCap software program for participant self-report and neuropsychological testing data has been finalized by the Boston University School of Public Health and is now ready for use, following several modifications: the addition of reference ranges for all lab sample values and the integration of neuropsychological questionnaires. All study personnel (including pharmacists) have received permission to access the software.

Preparation for study recruitment is also underway with the update of the study profile on clinicaltrials.gov. The study team has also exchanged recruitment strategies in anticipation of participant outreach, and a participant manual is also being organized to provide veterans with easy access to study-related information. These and other issues will continue to be discussed by the study team through established bimonthly conference calls, and further training in neuropsychological testing, REDCap use, and device operations for study staff will take place through both remote and in-person conferences. An operations manual for study staff is also currently being drafted to provide additional support when executing the study protocol.

Total enrollment to-date: 4 subjects.

REPORTABLE OUTCOMES

(none).

REFERENCES:

Anger WK, Storzbach D, Binder LM, Campbell KA, Rohlman DS, McCauley L, Kovera CA, Davis KL. (1999) Neurobehavioral deficits in Persian Gulf veterans: evidence from a population-based study. Portland Environmental Hazards Research Center. *J Int Neuropsychol Soc*, 5(3):203-12.

Chao LL, Abadjian L, Hlavin J, Meyerhoff DJ, Weiner MW. (2011, June 29). Effects of low -level sarin and cyclosarin exposure and Gulf War Illness on Brain Structure and Function: A study at 4T. *Neurotoxicology*.

Chao LL, Rothlind JC, Cardenas VA, Meyerhoff DJ, Weiner MW. (2010). Effects of low-level exposure to sarin and cyclosarin during the 1991 Gulf War on brain function and brain structure in US veterans. *Neurotoxicology*, 31(5):493-501.

Institute of Medicine (IOM). (2010). Gulf War and Health: Volume 8. Health Effects of Serving in the Gulf War. Washington, DC: *National Academies Press*.

Kang H, Li B, Mahan C, Eisen S, Engel C. (2009). Health of US Veterans of 1991 Gulf War: A follow up Survey in 10 years. *JOEM*, 51(4): 1-10.

Krengel M, Sullivan K. (2008). Neuropsychological Functioning in Gulf War veterans exposed to pesticides and pyridostigmine bromide. Fort Detrick, MD: *US Army Medical Research and Material Command*.

Li B, Mahan CM, Kang HK, Eisen SA, Engel CC. (2011, July 27). Longitudinal Health Study of US 1991 Gulf War Veterans: Changes in Health Status at 10-Year Follow-up. *Am J Epidemiol*.

Proctor SP, Heeren T, White RF, Wolfe J, Borgos MS, Davis JD, Pepper L, Clapp R, Sutker PB, Vasterling JJ, Ozonoff D. (1998). Health status of Persian Gulf War veterans: self-reported symptoms, environmental exposures and the effect of stress. *Int J Epidemiol*, 27(6):1000-10.

Research Advisory Committee (RAC) on Gulf War Veterans' Illnesses. (2008). Gulf War illness and the Health of Gulf War Veterans: Scientific Findings and Recommendations. Washington, DC: US GPO.

Sullivan K, Krengel M, Proctor SP, Devine S, Heeren T, White RF. (2003). Cognitive functioning in treatment-seeking Gulf War veterans: pyridostigmine bromide use and PTSD. *Journal of Psychopathology and Behavioral Assessment*. 25(2):95-103.

Tillman GD, Green TA, Ferree TC, Calley CS, Maguire MJ, Briggs R, Hart J Jr, Haley RW, Kraut MA. (2010, Oct 15). Impaired response inhibition in ill Gulf War veterans. *J Neurol Sci*, 297(1-2):1-5.

Toomey R, et al. (2009). Neuropsychological functioning of U.S. Gulf War veterans 10 years after the war. *Journal of the International Neuropsychological Society*, 15(5):717-29.